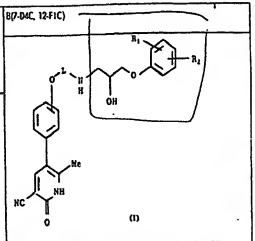
91-088849/13 603 GLAX 22.09.89
GUANO INC *EP -419-286-A
09.08.90-US-565297 (+US-4110655) (27.03.91) A61k-31/43
C07d-213/65

New phenoxy-substd. pyridone nitrile(s) - are used in treating cardiovascular disease, esp. congestive heart failure

C91-039751 R(AT BE CH DE DK ES FR GB GR IT LI LU NL SE)

Pyridone derivs. of formula (I) and their acid addn. salts are new:

B(7-D4C, 12-F1C)



(I)

R_1, R_2 = H, lower alkoxy, morpholino, CN, halo, CF_3.

EP-419286-A+

alkyl (opt. substd. by alkoxy or cycloalkylalkoxy), alkylsulphonyl, NO_2, OH, alkenyloxy, NH_2 or mono- or di-alkylamino;

L = $(CR_3R_4)_nCONH(R_5)CR_7R_8CR_9R_{10}$ (gp.(a)) or $(CR_{10}R_{11})_p$;

R_3 - R_{11} = independently H or lower alkyl;

n = 1-3;

p = 2-6.

MORE SPECIFICALLY

L = (a; n = 1-3) or (b; p = 3) and OL is at the 4-position.

R_3-R_{10} and R_{11} = H;

R_6 and R_9 = H or Me;

either

(1) R_1 = H;

R_2 = CN, Cl or Me;

(2) R_1 = H;

R_2 = H, CN or Cl at the 3-position.

USE

(1) are positive inotropic and β-adrenergic agents useful for treating congestive heart failure. Dose is 0.1-5 μg/kg 1-4 times a-day.

SPECIFICALLY CLAIMED

15 Cpds. (I) e.g. 5-(4-(N-(2-(3-phenoxy-2-hydroxypropylamino)ethyl)carbamoylmethoxy)phenyl)-6-methyl-2-oxo-1,2-dihydro-3- pyridinecarbonitrile (Ia);

5-(4-(N-(2-(3-(2-cyanophenoxy)-2S-hydroxypropylamino)-2-methylpropyl)carbamoylpropoxy) phenyl)-6-methyl-2-oxo-1,2-dihydro-3-pyridinecarbonitrile; and

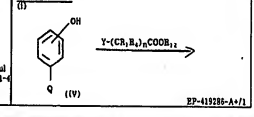
5-(4-(N-(2-(3-(2-chlorophenoxy)-2S-hydroxypropylamino)-2-methylpropyl)carbamoylmethoxy)phenyl)-6-methyl-2-oxo-1,2-dihydro-3-pyridinecarbonitrile.

WIDER DISCLOSURE

Intermediates of formula (VI), (VII), (X), (XVII) and (XVIII) are stated to form part of the invention.

PREPARATION

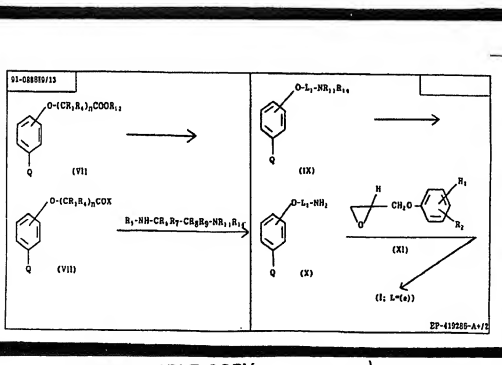
(I)



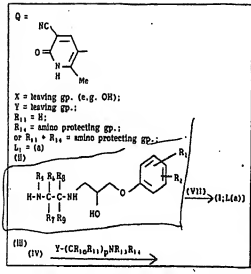
(IV)

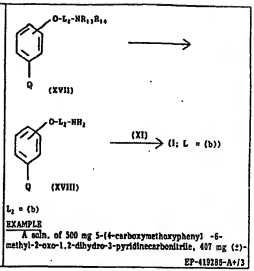
EP-419286-A+/1

91-088849/13



EP-419286-A+/2





EXAMPLE

A soln. of 300 mg 5-(4-carboxymethoxyphenyl -6-methyl-2-oxo-1,2-dihydro-3-pyridinecarbonitrile, 407 mg (±)-

91-088869/13

-N-(2-aminoethyl)-3-hydroxy-3-phenoxypropylamine and 316 mg diethyl cyanophosphonate in 10 ml DMF is cooled (ice bath) and treated dropwise with 540 µl Et_3N in 2 ml DMF. The mixt. is allowed to slowly warm to room temp.. stirred overnight under N_2 then evapd. in vacuo. The residue is chromatographed over silica gel, eluting with $CHCl_3$/MeOH/NH_4OH (90:10:2). The solid is recrystd. from EtOAc/MeOH to give 185 mg (21%) (Ia), m.pt. 135-138°C. (29pp815HBDwg%o0/0)

(E) ISR: No Search Report.